

Diffuse Optical Tomography of Breast Carcinoma:

Can Tumor Total Hemoglobin Concentration be Considered as a New Promising Prognostic Parameter of Breast Carcinoma?

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Rationale and Objectives: Diffuse optical tomography (DOT) is an emerging functional modality, which can reflect tumor metabolic activity and angiogenesis. The purpose of this exploratory study was to correlate the total hemoglobin concentration (THC) measured by noninvasive DOT with prognostic factors in breast carcinomas.

Materials and Methods: We prospectively imaged 251 breast carcinomas in 229 consecutive women (mean age, 51.18 ± 12.32 years) using DOT from 2007 to 2010. Tumor angiogenesis and metabolic activity were assessed based on quantitatively measured THC. The THC was correlated with prognostic factors, including tumor size, histopathologic classification, histologic grade, estrogen receptor (ER), progesterone receptor (PR), c-erbB-2, and p53.

Results: In univariate analysis, THC was significantly correlated with the following prognostic factors: tumor size ($P < .001$), histologic grade ($P < .001$), ER ($P < .05$), PR ($P < .001$), and c-erbB-2 ($P < .05$). THC was not associated with histopathologic classification ($P = .170$) or p53 ($P = .463$). On the basis of a stepwise multiple regression analysis, THC of invasive ductal carcinoma was significantly correlated with tumor size ($P < .001$), histologic grade ($P < .001$), and PR ($P < .05$).

Conclusions: THC was associated with prognostic factors of breast carcinoma. THC may be considered as a new prognostic parameter of breast carcinoma and a prediction of tumor behavior and biological activity.

Key Words: Breast carcinoma; total hemoglobin concentration; diffuse optical tomography; prognostic factors; angiogenesis.

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Ultrasound has been widely used as a screening and diagnostic modality to assess the morphologic characteristics of breast tumors. However, they do not provide information on physiological changes in lesions. Diffuse optical tomography (DOT) is an emerging functional modality, which is used for scanning multiwavelength diffuse scattering photons to acquire information on physiology, biochemistry, and molecular function of breast tumors (1) and give three-dimensional maps of absorption. DOT can measure the total hemoglobin concentration (THC) of breast lesions to quantitatively reflect tumor metabolic activity and angiogenesis, which are associated with prognosis in breast

carcinoma. Some researchers have used THC to differentiate breast carcinomas from benign lesions (1,2) and to monitor tumor changes during neoadjuvant chemotherapy (3). However, to our knowledge, there are few studies that have addressed the associations between THC and histopathologic prognostic factors of breast carcinoma (4,5). The purpose of our study was to investigate the correlation between THC and prognostic factors of breast carcinoma and the potential role of THC in predicting biological behavior preoperatively.

MATERIALS AND METHODS

Patients

The authors prospectively evaluated 546 lesions using ultrasound-guided DOT in 489 consecutive women who underwent open biopsy in our hospital between October 2007 and February 2010. The lesions were all identified using ultrasound at the time of the study. A total of 254 patients with 276 lesions were pathologically diagnosed with breast carcinomas. Eleven patients were excluded because their breast tissue was too thin to image (<1 cm), and 14 carcinomas were excluded because they had a large diameter

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(>5 cm), which caused poor probe-tissue contact and resulted in image artifacts. Thus, a total of 229 consecutive women (mean age, 51.18 ± 12.32 years; range, 19–82 years) with 251 breast carcinomas were included in the final study. The institutional review board approved this study, and all patients signed informed consent forms.

Ultrasound-guided DOT Imaging Methods

All breast lesions were examined using the OPTIMUS type II breast diagnostic system (XinaoMDT Technology Co, Ltd, China). This dual system contains a DOT system and ultrasound equipment with a linear 7–12 MHz transducer (Terason T3000 ultrasound; Teratech, Burlington, Massachusetts, USA).

The technical aspects of the DOT imaging system and data processing algorithm have been previously described in detail (1). Briefly, DOT uses near-infrared light sources to measure the functional parameters, THCs, of breast lesions. The THC was used to assess tumor angiogenesis. The ultrasound transducer in the middle of the combined probe was used to locate the lesions. Nine optical fibers (multimode regular fibers) used for emitting photons were on one side of the combined probe, and 10 optical detectors (Edmond Scientific, Fairfax, VA, USA) used for receiving photons were placed on the other side of the combined probe. The optical subsystem performed optical reconstruction using the frequency domain method. The light sources were modulated at a frequency of 100 MHz. We obtained the absorption coefficients at 785 and 830 nm by measuring the amplitude and phase. We selected the final reference data set on the basis of the linear fitting of the received amplitude and phase profiles (1). The DOT images were reconstructed from the optical data from 90 paths (nine fiber sources multiplied by 10 detectors) and the lesion size and location. The reconstruction process related the scattered field measured at the tissue surface to absorption variations in each voxel within the tissue using a Born approximation (6).

All DOT examinations were performed by two experienced physicians with 5 years of experience in breast ultrasonography. The process was as follows: first, optical scanning was performed by choosing the frame at the maximal diameter of the tumor as the optical horizontal plane. Then, the vertical plane optical data were acquired with the probe rotated at a 90° angle. Next, we performed the same process in the symmetric region of the contralateral breast, including the horizontal and vertical planes. The blood supply could be influenced by ipsilateral tumor. A normal site in the symmetrical region of the contralateral breast is more apt for comparison. Thus, the optical parameters of both the tumor and the normal breast tissue were acquired and recorded in the computer. After scanning the four planes (two lesion planes and two contralateral normal planes), the computer defined the region of interest according to the ultrasound imaging. The optical image was reconstructed by calculating the difference between the lesion and the symmetric region of the contralateral normal site. Optical characteristic parameters and the

THC value (micromoles per liter) were obtained at the same time. According to previous results, 140 $\mu\text{mol/L}$ was used as the threshold such that $\geq 140 \mu\text{mol/L}$ was considered as an abnormally high THC (1).

Histopathologic Analysis

All breast lesions in the study underwent surgical excision, and all lesions were histologically verified by the pathology department of our hospital. The breast carcinomas were histologically typed according to the WHO 2003 classification as follows: noninvasive (ductal carcinoma *in situ*; lobular carcinoma *in situ*) and invasive (invasive ductal carcinoma [IDC] not otherwise specified; invasive lobular carcinoma; medullary carcinoma; colloid carcinoma; tubular carcinoma; and other types).

The histologic grade of invasive ductal carcinoma (IDC) was assessed using the Nottingham combined histologic grade (Elston-Ellis modification of the Scarf-Bloom-Richardson grading system) (7). This scoring system evaluates the ductoglandular formation, nuclear pleomorphism, and mitotic activity. Grade I was considered well differentiated, grade II was moderately differentiated, and grade III was poorly differentiated.

Immunohistochemical Analysis

Immunohistochemical stains detected the expression status of estrogen receptor (ER), progesterone receptor (PR), c-erbB-2, and p53. Sections 4 μm thick were cut from paraffin blocks, deparaffinized, and then hydrated with ER, PR, c-erbB-2, or p53 microwave-treated antigen. Immunohistochemical stains used the DAKO (Dako Denmark A/S, Glostrup, Denmark) Envision two-step staining system. The evaluation of staining was performed as follows: (1) ER and PR were considered positive if the nuclei of breast cancer cells were stained. (2) The c-erbB-2 protein expression was semiquantitatively assessed and was classified into four categories (0, 1+, 2+, and 3+). Only the 3+ category was considered as positive (8). (3) If the cell nuclei were stained, p53 was considered positive.

Statistical Analysis

The software package SPSS for Windows 11.0 (SPSS Inc, Chicago, IL) was used for statistical data analysis. Continuous data were expressed as the means \pm standard deviation. To quantify the correlation between two continuous variables, the Student *t* test and Mann-Whitney test were used for normally and non-normally distributed data, respectively. When there were more than two groups, a one-way analysis of variance was used for normally distributed data and a Kruskal-Wallis test was used for non-normally distributed data. A Spearman rank correlation test was used to examine associations between two variables. $P < .05$ was considered statistically significant.

Univariate and multivariate statistical analyses were performed to explore the associations between THC and a series

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